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(54) Title: LEWIS ACID MEDIATED SYNTHESIS OF CYCLIC ESTERS

(57) Abstract: Methods for the synthesis of cyclic phosphonic acid diesters from 1,3-diols are described, whereby cyclic phosphonic acid diesters are produced by reacting a chiral 1,3-diol and an activated phosphonic acid in the presence of a Lewis acid.

LEWIS ACID MEDIATED SYNTHESIS OF CYCLIC ESTERS

RELATED APPLICATIONS

This application relates and claims benefit of U.S. Provisional Application Serial No. 60/578,467 filed on June 8, 2004, all of which is incorporated by reference in its entirety.

FIELD OF INVENTION

The present invention is directed towards a process of synthesis of cyclic phosphonic acid diesters from 1,3-diols. More specifically, the invention relates to an improved process wherein diastereoselectivity is increased during coupling a 1-arylpropane-1,3-diol with an activated phosphonic acid.

BACKGROUND OF THE INVENTION

The following description of the background of the invention is provided to aid in understanding the invention, but is not admitted to be, or to describe, prior art to the invention. All publications are incorporated by reference in their entirety.

Compounds containing phosphonic acids and their salts are highly charged at physiological pH and therefore frequently exhibit poor oral bioavailability, poor cell penetration and limited tissue distribution (*e.g.*, CNS). In addition, these acids are also commonly associated with several other properties that hinder their use as drugs, including short plasma half-life due to rapid renal clearance, as well as toxicities (*e.g.*, renal, gastrointestinal, etc.) (*e.g.*, Bijsterbosch *et al., Antimicrob. Agents Chemother.* 42(5): 1146-50 (1998)).

Phosphonic acid ester prodrugs can be used to improve the oral bioavailability, cell penetration and tissue distribution of drugs containing a phosphonic acid moiety.

The most commonly used prodrug class is the acyloxyalky ester, which was first applied to phosphate and phosphonate compounds in 1983 by Farquhar *et al., J. Pharm. Sci.* 72: 324 (1983). This strategy has proven successful in the delivery of phosphates and phosphonates into cells and in the oral absorption of phosphates, phosphonates and phosphinic acids. For example, the bis(pivoyloxymethyl) prodrug of the antiviral phosphonate, 9-(2-phosphonylmethoxyethyl)adenine (PMEA), has been studied clinically for the

treatment of CMV infection and the bis(pivaloyloxymethyl) prodrug of the squalene synthetase inhibitor, BMS188494 has been evaluated as a treatment of hypercholesterolemia and associated cardiovascular diseases. The marketed antihypertensive, fosinopril, is a phosphinic acid angiotensin converting enzyme inhibitor that requires the use of an isobutryloxyethyl group for oral absorption. A close variant of the acyloxyalkyl ester strategy is the use of alkoxycarbonyloxyalkyl groups as prodrugs. These prodrugs are reported to enhance oral bioavailability.

Other examples of suitable phosphonate prodrugs include proester classes exemplified by Krise *et al.* (*Adv. Drug Del. Rev.* 19: 287 (1996)); and Biller and Magnin (U.S. Patent No. 5,157,027).

Cyclic phosphonate esters have also been shown to decrease serum lipids and treat atherosclerosis (U.S. No. 5,962,440). Other examples of phosphonate esters are exemplified by Prisbe *et al.* (*J. Med. Chem.* 29: 671 (1986)); and Ozoe *et al.* (*Bioorg. Med. Chem.* 6: 73 (1998).

SUMMARY OF THE INVENTION

The present invention is directed towards a Lewis acid catalysis process for the synthesis of a cyclic phosphonic acid diester from a 1,3-diol and an activated phosphonic acid. In one aspect, methods are described that enable diastereoselective preparation of these products. In another aspect, the methods can also be used to prepare chiral substituted cyclic phosphonic acid (or phosphonate) diesters.

One aspect of the invention concerns a method of preparing a cyclic phosphonic acid diester via reacting a chiral 1,3-diol and an activated phosphonic acid in the presence of a Lewis acid. In a further aspect, the Lewis acid is added to the chiral 1,3-diol and the diol-Lewis acid complex is added to the activated phosphonic acid.

In an additional aspect, the ratio of *cis*- to *trans*- diastereomers formed is greater than or equal to 3:1.

Also provided are methods where the Lewis acid contains an element selected from the group consisting of titanium, tin, aluminum, zinc, boron, magnesium, samarium, bismuth, iron, mercury, copper, silver and cobalt. In an additional aspect, the Lewis acid contains an element selected from the group

consisting of titanium, boron, aluminum, tin, and samarium. In a further aspect, the Lewis acid contains a group independently selected from alkoxy, alkyl, aryl, or an inorganic radical. In another aspect, the Lewis acid contains a group independently selected from alkoxy, alkyl, aryl, or an inorganic radical, where the inorganic radical is selected from the group consisting of chloride, iodide, bromide, and fluoride. In a further aspect, the Lewis acid is selected from $TiCl_4$, BF_3, $SnCl_4$, SmI_2, and $AlCl_3$. An additional aspect the Lewis acid is $TiCl_4$. In a further aspect the Lewis acid is $Ti(O\text{-}(C_1\text{-}C_4)alkyl)_4$.

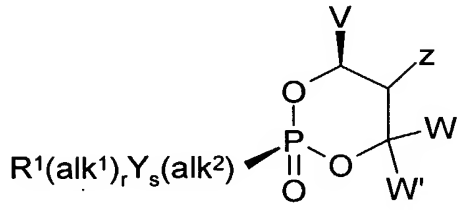
Also provided are methods where the activated phosphonic acid is phosphonic acid halide, phosphonic acid anhydride, or phosphonic acid carbonate. In another aspect, the activated phosphonic acid is phosphonic acid halide. In a further aspect, the phosphonic acid halide is phosphonyl chloride.

In another aspect, the method provides for adding a base selected from tertiary alkyl amines, N-containing heterocyclic aromatic bases, and non-nucleophilic inorganic bases. In a further aspect, the base is triethylamine, tri(n-butyl)amine, pyridine, quinoline or diisopropylethylamine.

In one aspect, the temperature for the reaction is -78 °C and 60 °C. In another aspect, the temperature is between -20 °C and 50 °C. In a further aspect, the temperature is between 15 °C and 42 °C.

In one aspect, the reaction is carried out by adding 0.01 to 5 equivalents of said Lewis acid to 1.0 equivalent of said chiral 1,3-diol. In a further aspect, 0.5 to 2.0 equivalents of said Lewis acid is added.

One aspect of the invention concerns the method for the preparation of compounds of Formula I:



Formula I

wherein:

V is selected from group consisting of phenyl, allyl, alkynyl, and monocyclic heteroaryl, all optionally substituted with 1-4 substituents;

R^1 is selected from the group consisting of hydrogen, optionally substituted aryl, optionally substituted heteroaryl, or

R^1 is a group of the formula Ar^1-G-Ar^2, wherein Ar^1 and Ar^2 are aryl groups optionally substituted by lower alkyl, lower alkoxy, halogen, hydroxy, cyano, and amino, and G is -O-, -S-, -S(=O)-, -$S(=O)_2$-, -CH_2-, -CF_2-, -CHF-, -C(O)-, -CH(OH)-, -NH-, and -N(C_1-C_4 alkyl)-;

alk^1 and alk^2 are the same or different and are each optionally-substituted lower alkylene;

Y is selected from the group consisting of –O-, -S-, -NR^2-, -C(O)-, -C(O)NR^2, and -NR^2C(O)-;

W and W' are independently selected from the group consisting of H, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted monocyclic aryl, and optionally substituted monocyclic heteroaryl;

Z is selected from the group consisting of halogen, -CN, -COR^3, -$CONR^4_2$,
-CO_2R^3, -$CHR^2OC(O)R^3$, -$CHR^2OC(S)R^3$, -$CHR^2OC(O)SR^3$, -$CHR^2OCO_2R^3$, -OR^3,
-SR^3, -R^2, -NR^3_2, -$OCOR^3$, -OCO_2R^3, -$SCOR^3$, -SCO_2R^3, -$(CH_2)_p$-OR^4, and -$(CH_2)_p$-SR^4;

R^2 is hydrogen or lower alkyl;

R^3 is alkyl;

R^4 is alkyl or acyl;

p is 2 or 3;

r is 0 or 1; and

s is 0 or 1.

In a further aspect, the hydroxy groups present in the formula Ar^1-G-Ar^2 may be protected.

In another aspect, said 1-(aryl)-1,3-propane diol is added to the Lewis acid and then the diol-Lewis acid complex is added to $R^1(alk^1)_rY_s(alk^2)P(O)Cl_2$ in the presence of said base.

In an additional aspect the method of preparation for compounds of Formula I provides for an increased ratio of *cis* to *trans* diastereomers. In an

additional aspect, the ratio of *cis*- to *trans*- diastereomers formed is greater than or equal to 3:1.

Also provided are methods where the Lewis acid contains an element selected from the group consisting of titanium, tin, aluminum, zinc, boron, magnesium, samarium, bismuth, iron, mercury, copper, silver and cobalt. In an additional aspect, the Lewis acid contains an element selected from the group consisting of titanium, boron, aluminum, tin, and samarium. In a further aspect, the Lewis acid contains a group independently selected from alkoxy, alkyl, aryl, or an inorganic radical. In another aspect, the Lewis acid contains a group independently selected from alkoxy, alkyl, aryl, or an inorganic radical, where the inorganic radical is selected from the group consisting of chloride, iodide, bromide, and fluoride. In a further aspect, the Lewis Acid is selected from $TiCl_4$, BF_3, $SnCl_4$, SmI_2, and $AlCl_3$. In an additional aspect, the Lewis acid is $TiCl_4$. In a further aspect, the Lewis acid is $Ti(O\text{-}(C_1\text{-}C_4)alkyl)_4$.

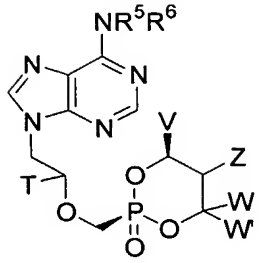
In another aspect, the method provides for adding a base selected from tertiary alkyl amines, N-containing heterocyclic aromatic bases, and non-nucleophilic inorganic bases. In a further aspect the base is triethylamine, tri(n-butyl)amine, pyridine, quinoline or diisopropylethylamine.

In one aspect, the temperature for the reaction is -78 °C and 60 °C. In another aspect the temperature is between -20 °C and 50 °C. In a further aspect, the temperature is between 15 °C and 42 °C.

In one aspect, the reaction is carried out by adding 0.01 to 5 equivalents of said Lewis acid to 1.0 equivalent of said chiral 1,3-diol. In a further aspect, 0.5 to 2.0 equivalents of said Lewis acid is added.

Some of the compounds of Formula I have asymmetric centers where the stereochemistry is unspecified and the diastereomeric mixtures of these compounds are included as well as the individual stereoisomers when referring to a compound of Formula I generally.

In another aspect, the invention relates to a method for the preparation of compounds of Formula II:



Formula II

wherein,

V is selected from group consisting of aryl, and monocyclic heteroaryl, all optionally substituted with 1-4 substituents;

W and W' are independently selected from the group consisting of H, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted monocyclic aryl, and optionally substituted monocyclic heteroaryl;

Z is selected from the group consisting of halogen, -CN, $-COR^3$, $-CONR^4_2$,
$-CO_2R^3$, $-CHR^2OC(O)R^3$, $-CHR^2OC(S)R^3$, $-CHR^2OC(O)SR^3$, $-CHR^2OCO_2R^3$, $-OR^3$,
$-SR^3$, $-R^2$, $-NR^3_2$, $-OCOR^3$, $-OCO_2R^3$, $-SCOR^3$, $-SCO_2R^3$, $-(CH_2)_p-OR^4$, and $-(CH_2)_p-SR^4$;

T is selected from the group consisting of H and lower alkyl;

R^2 is hydrogen or lower alkyl;

R^3 is alkyl;

R^4 is alkyl or acyl;

p is 2 or 3;

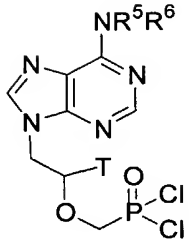
r is 0 or 1; and

s is 0 or 1;

R^5 is a monovalent amine protecting group, and R^6 is hydrogen; or,

R^5 and R^6 taken together are a divalent amine protecting group.

In another aspect, the method of preparing a compound of Formula II includes combining a 1-(V)-1,3-propane diol with a compound of Formula III in the presence of a Lewis acid:



Formula III

In an additional aspect the method of preparation for compounds of Formula II provides for an increased ratio of *cis* to *trans* diastereomers. In an additional aspect, the ratio of *cis*- to *trans*- diastereomers formed is greater than or equal to 3:1.

Also provided are methods where the Lewis acid contains an element selected from the group consisting of titanium, tin, aluminum, zinc, boron, magnesium, samarium, bismuth, iron, mercury, copper, silver and cobalt. In an additional aspect, the Lewis acid contains an element selected from the group consisting of titanium, boron, aluminum, tin, and samarium. In a further aspect, the Lewis acid contains a group independently selected from alkoxy, alkyl, aryl, or an inorganic radical. In another aspect, the Lewis acid contains a group independently selected from alkoxy, alkyl, aryl, or an inorganic radical, where the inorganic radical is selected from the group consisting of chloride, iodide, bromide, and fluoride. In a further aspect, the Lewis Acid is selected from $TiCl_4$, BF_3, $SnCl_4$, SmI_2, and $AlCl_3$. An additional aspect the Lewis acid is $TiCl_4$. In a further aspect, the Lewis acid is $Ti(O\text{-}(C_1\text{-}C_4)alkyl)_4$.

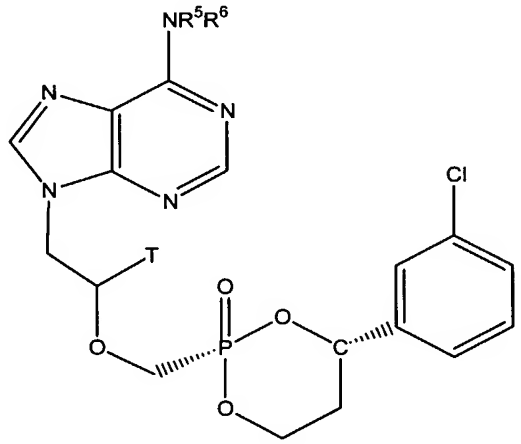
In another aspect, the method provides for adding a base selected from tertiary alkyl amines, N-containing heterocyclic aromatic bases, and non-nucleophilic inorganic bases. In a further aspect the base is triethylamine, tri(n-butyl)amine, pyridine, quinoline or diisopropylethylamine.

In one aspect, the temperature for the reaction is -78 °C and 60 °C. In another aspect the temperature is between -20 °C and 50 °C. In a further aspect, the temperature is between 15 °C and 42 °C.

In one aspect, the reaction is carried out by adding 0.01 to 5 equivalents of said Lewis acid to 1.0 equivalent of said chiral 1,3-diol. In a further aspect, 0.5 to 2.0 equivalents of said Lewis acid is added.

Some of the compounds of Formula II have asymmetric centers where the stereochemistry is unspecified and the diastereomeric mixtures of these compounds are included as well as the individual stereoisomers when referring to a compound of Formula II generally.

The present invention provides a method for the preparation of compounds of Formula IV:



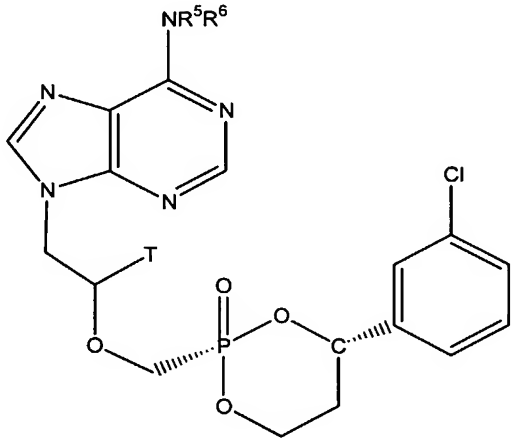
Formula IV

wherein R^5 is *tert*-butyloxycarbonyl, benzyloxycarbonyl, trifluoroacetyl or benzyl; and R^6 is hydrogen; or,

R^5 and R^6 taken together are phthalimidoyl, phenylmethylidene, dimethylaminomethylidene and diethylaminomethylidene; and

T is selected from the group consisting of H and lower alkyl.

An additional aspect provides a method for the preparation of compounds of Formula IV:



Formula IV

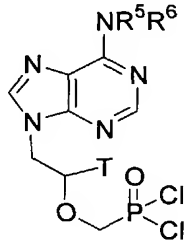
wherein R^5 is *tert*-butyloxycarbonyl, benzyloxycarbonyl, trifluoroacetyl or benzyl; and R^6 is hydrogen; or,

R^5 and R^6 taken together are phthalimidoyl, phenylmethylidene, dimethylaminomethylidene and diethylaminomethylidene;

T is selected from the group consisting of H and lower alkyl;

comprising:

combining (*R*)-1-(3-chlorophenyl)-1,3-propanediol with a compound of Formula III in the presence of a Lewis acid.



Formula III

In a further aspect of the preparation of compounds of Formula IV said (*R*)-1-(3-chlorophenyl)-1,3-propanediol is added to the Lewis acid and then the diol-Lewis acid complex is added to the compound of Formula III.

In an additional aspect, the method of preparation for compounds of Formula IV provides for an increased ratio of *cis* to *trans* diastereomers. In an additional aspect, the ratio of *cis*- to *trans*- diastereomers formed is greater than or equal to 3:1.

Also provided are methods where the Lewis acid contains an element selected from the group consisting of titanium, tin, aluminum, zinc, boron, magnesium, samarium, bismuth, iron, mercury, copper, silver and cobalt. In an additional aspect, the Lewis acid contains an element selected from the group consisting of titanium, boron, aluminum, tin, and samarium. A further aspect the Lewis acid contains a group independently selected from alkoxy, alkyl, aryl, or an inorganic radical. In another aspect, the Lewis acid contains a group independently selected from alkoxy, alkyl, aryl, or an inorganic radical, where the inorganic radical is selected from the group consisting of chloride, iodide, bromide, and fluoride. In a further aspect, the Lewis Acid is selected from $TiCl_4$, BF_3, $SnCl_4$, SmI_2, and $AlCl_3$. In an additional aspect, the Lewis acid is $TiCl_4$. In a further aspect, the Lewis acid is $Ti(O\text{-}(C_1\text{-}C_4)alkyl)_4$.

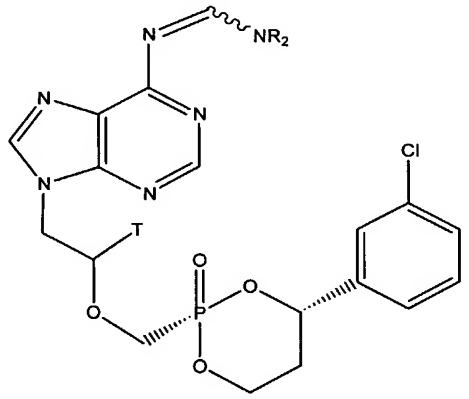
In another aspect, the method provides for adding a base selected from tertiary alkyl amines, N-containing heterocyclic aromatic bases, and non-nucleophilic inorganic bases. In a further aspect, the base is triethylamine, tri(n-butyl)amine, pyridine, quinoline or diisopropylethylamine.

In one aspect, the temperature for the reaction is -78 °C and 60 °C. In another aspect the temperature is between -20 °C and 50 °C. In a further aspect, the temperature is between 15 °C and 42 °C.

In one aspect, the reaction is carried out by adding 0.01 to 5 equivalents of said Lewis acid to 1.0 equivalent of said chiral 1,3-diol. In a further aspect, 0.5 to 2.0 equivalents of said Lewis acid is added.

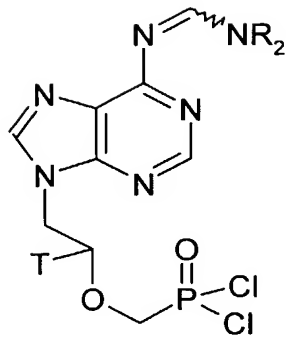
Some of the compounds of Formula IV have asymmetric centers where the stereochemistry is unspecified and the diastereomeric mixtures of these compounds are included as well as the individual stereoisomers when referring to a compound of Formula IV generally.

A further aspect the invention provides a method for the preparation of compounds of Formula V:



Formula V

wherein R is lower alkyl and T is selected from the group consisting of H and lower alkyl. In one aspect (*R*)-1-(3-chlorophenyl)-1,3-propanediol is combined with a compound of Formula VI in the presence of a Lewis acid:



Formula VI

In a further aspect of the preparation of compounds of Formula IV said (*R*)-1-(3-chlorophenyl)-1,3-propanediol is added to the Lewis acid and then the diol-Lewis acid complex is added to the compound of Formula VI.

In an additional aspect the method of preparation for compounds of Formula V provides for an increased ratio of *cis* to *trans* diastereomers. In an additional aspect, the ratio of *cis*- to *trans*- diastereomers formed is greater than or equal to 3:1.

Also provided are methods where the Lewis acid contains an element selected from the group consisting of titanium, tin, aluminum, zinc, boron, magnesium, samarium, bismuth, iron, mercury, copper, silver and cobalt. In an additional aspect, the Lewis acid contains an element selected from the group consisting of titanium, boron, aluminum, tin, and samarium. In a further aspect, the Lewis acid contains a group independently selected from alkoxy, alkyl, aryl, or an inorganic radical. In another aspect, the Lewis acid contains a group independently selected from alkoxy, alkyl, aryl, or an inorganic radical, where the inorganic radical is selected from the group consisting of chloride, iodide, bromide, and fluoride. In a further aspect, the Lewis Acid is selected from $TiCl_4$, BF_3, $SnCl_4$, SmI_2, and $AlCl_3$. In an additional aspect, the Lewis acid is $TiCl_4$. In a further aspect, the Lewis acid is $Ti(O\text{-}(C_1\text{-}C_4)alkyl)_4$.

In another aspect, the method provides for adding a base selected from tertiary alkyl amines, N-containing heterocyclic aromatic bases, and non-nucleophilic inorganic bases. In a further aspect, the base is triethylamine, tri(n-butyl)amine, pyridine, quinoline or diisopropylethylamine.

In one aspect, the temperature for the reaction is -78 °C and 60 °C. In another aspect, the temperature is between -20 °C and 50 °C. In a further aspect the temperature is between 15 °C and 42 °C.

In one aspect, the reaction is carried out by adding 0.01 to 5 equivalents of said Lewis acid to 1.0 equivalent of said chiral 1,3-diol. In a further aspect, 0.5 to 2.0 equivalents of said Lewis acid is added.

Some of the compounds of Formula V have asymmetric centers where the stereochemistry is unspecified and the diastereomeric mixtures of these compounds are included as well as the individual stereoisomers when referring to a compound of Formula V generally.

Additionally, methods and salt forms are described that enable isolation and purification of the desired isomer.

Definitions

In accordance with the present invention and as used herein, the following terms are defined with the following meanings, unless explicitly stated otherwise.

The term "hexanes" refers to commercially available HPLC reagent solutions which contains approximately 95% hexane, methylcyclopropane, and methylpentane.

The term "dialkyl" refers to a compound containing two alkyl groups. The term "alkyl" refers to saturated aliphatic groups including straight-chain, branched chain and cyclic groups. Suitable alkyl groups include methyl, ethyl, isopropyl, and cyclopropyl.

The term "alkylene" refers to a divalent straight chain, branched chain or cyclic saturated aliphatic group. In one aspect the alkylene group contains up to and including 10 atoms. In another aspect the alkylene chain contains up to and including 6 atoms. In a further aspect the alkylene groups contains up to and including 4 atoms. The alkylene group can be either straight, branched, unsaturated, or cyclic. The alkylene may be optionally substituted with 1-3 substituents.

The term "aryl" refers to aromatic groups which have 5-14 ring atoms and at least one ring having a conjugated pi electron system and includes carbocyclic aryl, heterocyclic aryl and biaryl groups, all of which may be optionally substituted.

Heterocyclic aryl or heteroaryl groups are groups which have 5-14 ring atoms wherein 1 to 4 of the ring atoms are heteroatoms with the remainder of the ring atoms being carbon atoms. Suitable heteroatoms include oxygen, sulfur, nitrogen, and selenium. Suitable heteroaryl groups include furanyl, thienyl, pyridyl, pyrrolyl, N-lower alkyl pyrrolyl, pyridyl-N-oxide, pyrimidyl, pyrazinyl, imidazolyl, adeninyl, thyminyl, cytosinyl, guaninyl, uracilyl, and the like, all optionally substituted.

The term "monocyclic aryl" refers to aromatic groups which have 5-6 ring atoms and includes carbocyclic aryl and heterocyclic aryl. Suitable aryl groups include phenyl, furanyl, pyridyl, and thienyl. Aryl groups may be substituted.

The term "monocyclic heteroaryl" refers to aromatic groups which have 5-6 ring atoms wherein 1 to 4 heteroatoms are ring atoms in the aromatic ring and the remainder of the ring atoms being carbon atoms. Suitable heteroatoms include oxygen, sulfur, and nitrogen.

The term monovalent nitrogen protecting group refers to a protecting group that is attached to nitrogen by a single bond. Examples include but are not limited to *tert*-butyloxycarbonyl, benzyloxycarbonyl, trifluoroacetyl and benzyl.

The term divalent nitrogen protecting group refers to a protecting group that is attached to nitrogen either by two single bonds or by a double bond. Examples include but are not limited to phthalimidoyl, phenylmethylidene, dimethylaminomethylidene and diethylaminomethylidene.

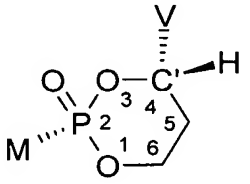
The term "optionally substituted" or "substituted" includes aryl groups substituted by one to four substituents, independently selected from lower alkyl, lower aryl, and halogens. In one aspect these substituents are selected from the group consisting of halogens.

The term 'chiral' refers to an object or molecule that is not superimposable upon its mirror image.

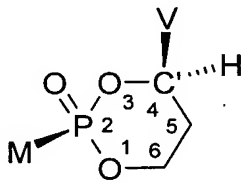
The term 'diastereoselective' refers to a reaction in which two or more diastereomers may be formed wherein unequal amounts of the diastereomers are obtained. If two diastereomers are formed, typically the ratio of diastereomers is at least 2:1.

The term 'Lewis acid' refers to any species that can accept a pair of electrons and form a coordinate covalent bond.

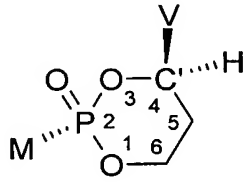
The term "*cis*" stereochemistry refers to the relationship of the V group and M group positions on the six-membered ring. V and M are said to be located *cis* to each other if they lie on the same side of the plane. The formula below shows a *cis* stereochemistry.



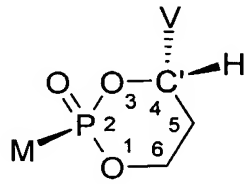
Another *cis* stereochemistry would have V and M pointing above the plane. The formula below shows this *cis* stereochemistry.



The term "*trans*" stereochemistry refers to the relationship of the V group and M group positions on the six-membered ring. V and M are said to be located *trans* to each other if they lie on opposite side of the plane. The formula below shows a *trans* stereochemistry.

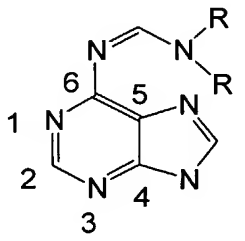


Another *trans* stereochemistry would have M pointing above the plane and V pointing below the plane. The formula below shows this *trans* stereochemistry.

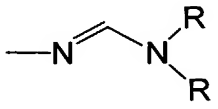


The term "N6-substituted" refers to the substitution at the amine attached at the 6-position of a purine ring system. N6- is generally substituted with an

amine protecting group. Examples include the dialkylaminomethylene group, BOC, CBz, trityl as well as divalent groups like phthalimidoyl.



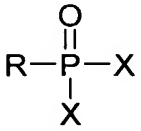
The terms "N,N-dialkylaminomethyleneimine," "N,N-dialkylaminomethylene" and "N,N-dialkylaminomethylidene" refer to the functional group or substitution of the following structure



wherein R groups include but are not limited to C1-C4 acyclic, alkyl , C5-C6 cyclic alkyl, benzyl, phenethyl, or R groups together form piperdine, morpholine, and pyrrolidine.

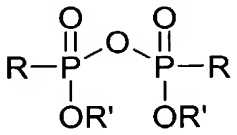
The term "nitrogen protecting group" refers to R group and includes but is not limited to BOC, CBz, trityl, , N,N-dialkylaminomethylidene, phthalimidoyl, or other monovalent and divalent groups.

The term "phosphonic acid halide" refers to a phosphonic acid wherein the two OH groups have been replaced by halogen atoms. The formula below shows this structure

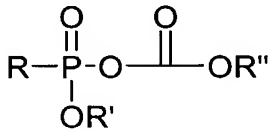


The term "phosphonic acid anhyride" refers to a compound that is formed by combining two moles of phosphonic acid with the removal of one mole of water.

The formula below shows an example of this structure



The term "phosphonic acid carbonate" refers to a phosphonic acid wherein one OH groups has been replaced by a carbonate group. The formula below shows an example of this structure



The term "percent enantiomeric excess (% ee)" refers to optical purity. It is obtained by using the following formula:

$$\frac{[R]-[S]}{[R]+[S]} \times 100 = \%R - \%S$$

where [R] is the amount of the R isomer and [S] is the amount of the S isomer. This formula provides the % ee when R is the dominant isomer.

The term "d.e." refers to diastereomeric excess. It is obtained by using the following formula:

$$\frac{[cis]-[trans]}{[cis]+[trans]} \times 100 = \%[cis] - \%[trans]$$

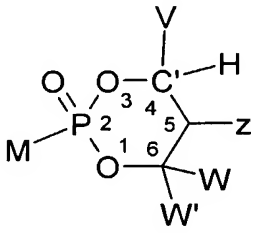
The term "diastereoisomer" refers to compounds with two or more asymmetric centers having the same substituent groups and undergoing the same types of chemical reactions wherein the diasteroismers have different physical properties, have substituent groups which occupy different relative positions in space, and have different biological properties.

The term "racemic" refers to a compound or mixture that is composed of equal amounts of dextrorotatory and levorotatory forms of the same compound and is not optically active.

The term "enantiomer" refers to either of a pair of chemical compounds whose molecular structures have a mirror-image relationship to each other.

The term "halogen" refers to chloride, bromide, iodide, or fluoride.

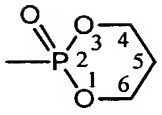
The term "prodrug" as used herein refers to any M compound that when administered to a biological system generates a biologically active compound as a result of spontaneous chemical reaction(s), enzyme catalyzed chemical reaction(s), and/or metabolic chemical reaction(s), or a combination of each. Standard prodrugs are formed using groups attached to functionality, *e.g.*, HO-, HS-, HOOC-, R_2N-, associated with the drug that cleave *in vivo*. Standard prodrugs include but are not limited to carboxylate esters where the group is alkyl, aryl, aralkyl, acyloxyalkyl, alkoxycarbonyloxyalkyl as well as esters of hydroxyl, thiol and amines where the group attached is an acyl group, an alkoxycarbonyl, aminocarbonyl, phosphate or sulfate. The groups illustrated are exemplary, not exhaustive, and one skilled in the art could prepare other known varieties of prodrugs. Such prodrugs of the compounds of formula A, fall within the scope of the present invention. Prodrugs must undergo some form of a chemical transformation to produce the compound that is biologically active or is a precursor of the biologically active compound. In some cases, the prodrug is biologically active, usually less than the drug itself, and serves to improve drug efficacy or safety through improved oral bioavailability, pharmacodynamic half-life, *etc.* The biologically active compounds



Formula A

include, for example, anticancer agents, and antiviral agents.

The term "cyclic phosphate ester of 1,3-propanediol", "cyclic phosphate diester of 1,3-propanediol", "2 oxo $2\lambda^5$ [1,3,2] dioxaphosphorinane", "2-oxo-[1,3,2]- dioxaphosphorinane", or "dioxaphosphorinane" refers to the following:



The term "enhancing" refers to increasing or improving a specific property.

The term "enriching" refers to increasing the quantity of a specific isomer produced by a reaction.

The term "non-nucleophilic inorganic base" refers to an inorganic base that has low potential to react with electrophiles. Examples of non-nucleophilic inorganic bases include sodium bicarbonate, sodium carbonate, and potassium carbonate.

The term "activated phosphonic acid" refers to a phosphonic acid wherein the two OH groups have been replaced by leaving groups, such as halogen atoms.

The following well known chemicals are referred to in the specification and the claims. Abbreviations and common names are also provided.

BOC; *tert*-butoxycarbonyl group

CBz; benzyl carbamate

Trityl; triphenylmethyl group

CH_2Cl_2; dichloromethane or methylene chloride

DCM; dichloromethane

(-)-DIP-Cl; (-)-β-chlorodiisopinocampheylborane

DMAP; 4-dimethylaminopyridine

DMF; dimethylformamide

HCl; hydrochloric acid

KI; potassium iodide

$MgSO_4$; magnesium sulfate

MTBE; *t*-butyl methyl ether

NaCl; sodium chloride

NaOH; sodium hydroxide

PyBOP; benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate

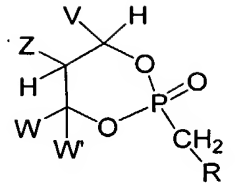
TEA; triethylamine
THF; tetrahydrofuran
TMSCl; chlorotrimethylsilane
TMEDA; tetramethylethlenediamine
EDTA; ethylenediaminetetraacetic acid.

The following well known drugs are referred to in the specification and the claims. Abbreviations and common names are also provided.

PMEA; 9-(2-phosphonylmethoxyethyl)adenine (Adefovir)
(R)-PMPA; (R)-9-(2-phosphonylmethoxypropyl)adenine (Tenofovir)
(R)-PMPDAP; (R)-9-(2-phosphonylmethoxypropyl)-2,-6-diaminopurine
FPMPDAP; 9-[(2RS)-3-fluoro-2-phosphonylmethoxypropyl]-2,6-diaminopurine
FPMGP; 9-[(2RS)-3-fluoro-2-phosphonylmethoxypropyl]guanine
(S)-HPMPDAP; 9-=[2S]-3-hydroxy-2-phosphonylmethoxylpropyl]-2,6-diaminopurine
PMEG; 9-(2-phosphonylmethoxyethyl)guanine
PMEI; 2-phosphonylmethoxyethyl-6-oxopurine
PMEMAP; 9-(2-phosphonylmethoxyethyl)2-aminopurine
PMET; 2-phosphonylmethoxyethyl-thymine

DETAILED DESCRIPTION OF THE INVENTION

This invention is directed to the discovery that the utilization of Lewis acid catalysis in the coupling process during the synthesis of cyclic 1,3-propanyl esters of phosphonyl compounds enhanced the ratio of diastereomers of the resultant product. In one aspect the invention is directed towards the utilization of Lewis acid catalysis in the coupling process during the synthesis of cyclic 1-aryl-1,3-propanyl esters of phosphonyl compounds. Compounds synthesized by the process of the present invention are directed towards cyclic esters of phosphonic acids as shown in the following formula:



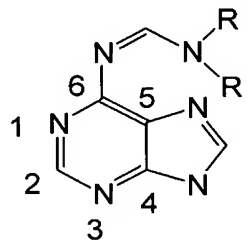
Formula W

Cyclic ester prodrugs of phosphonic acids have been demonstrated to be useful in improving the oral bioavailability of drugs containing a phosphonic acid moiety, and in increasing the concentration of the active drug in the liver (U.S. Patent No. 6,312,662). The cyclic 1,3-propanyl-1-aryl phosphonate cyclic esters of PMEA and related analogs having *cis* relative stereochemistry have been shown to be able to treat diseases of the liver (U.S. PreGrant Published Application 2003/0229225 A1). These compounds enhance the oral delivery and/or prolong the pharmacodynamic half-life of PMEA and like analogs. In addition, the compounds achieve targeted delivery of PMEA to the liver and increase the therapeutic index of the drug.

The aforementioned prodrugs have been made in a modestly stereoselective manner by coupling a chiral 1,3-diol with a phosphonic acid dichloridate at low temperature (U.S. PreGrant Published Application 2003/0225277 A1). The dichloridate of PMEA is readily prepared using standard chlorination conditions. The coupling reaction with the dichloridate at low temperature was complicated by the poor solubility of the dichloridate. It was found that by adding a protected form of the dichloridate to the diol at low temperatures a diastereoselectivity of 50 % could be achieved.

Lewis acids have been used to improve the diastereoselectivity of chemical reactions. For example, titanium tetrachloride has been used to enhance the diastereoselectivity of enolate aldol reactions (Evans *et. al., J. Am. Chem. Soc.* 112: 8215 (1990); Evans *et. al., J. Am. Chem. Soc.* 113: 1047 (1991)). It has been proposed that a six membered transition state is the controlling factor of the enhanced diastereoselectivity. It has also been shown that titanium tetrachloride can be used as a catalyst for phosphoryl transfer (Jones *et. al., Org. Lett.* 4: 3671 (2002)). However, Lewis acids have not been reported to improve the diastereoselectivity of formation of cyclic phosphonic esters; this application describes such an invention.

During the coupling reaction functional groups on the R as shown in the above Formula W, such as amines and hydroxyl groups, may be protected with a variety of amine protecting groups. An example of use of the dialkylamine methylidene group (N,N-dialkylaminomethylene and N,N-dialkylaminomethylidene) is shown below with the nitrogen attached to the carbon labeled 6 protected in the structure below.



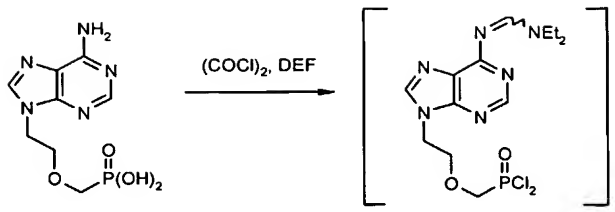
The process for the synthesis of cyclic 1,3-propanyl esters with the desired stereochemistry is via a convergent synthetic sequence. The final resultant compound contained two stereocenters, (1) the methine carbon which is identified as C4′ in the steroisomeric structures and (2) the phosphorus of the cyclic phosphonate ring.

The phosphorus chirality was the result of the diastereoselective coupling of the parent phosphonic acid and the chiral diol. The desired *cis* isomer, wherein *cis* refers to the isomeric relationship between the phosphorus-carbon bond and the carbon-aryl bond of the cyclic phosphonate ring, was isolated via a selective crystallization of the acid salt.

Compounds Prepared by the Invention

1. Synthesis of N6-protected PMEA-dichloridate:

Chlorination of PMEA is achieved using oxalyl chloride and N,N-diethylformamide to give N6 protected-PMEA-dichloridate. N,N-dialkylformamide used in the chlorination step not only forms a Vilsmeyer chlorinating agent, but also protects the NH_2 group at the 6 position.



2. Coupling of Phosphonic Dichloridate and Chiral Diol:

2.1 Effect of dichloridate addition order and temperature.

Earlier work (U.S. 2003225277 A1) had shown that the coupling of the protected phosphonic acid dichloridate and diol can be accomplished by low temperature addition to the diol in the presence of base. This led to a modest d.e. of 50 % and required conducting the reaction at low temperatures.

Unexpectedly and surprisingly, the inventors observed improved d.e.'s when this low temperature coupling was done in the presence of a Lewis acid. Changes were made to the order of addition of the reagents (see Table 1). When the solution of the diol and base was added to a mixture of the dichloridate and Lewis acid, the results were similar to those obtained above. When a complex of the diol and Lewis acid was added to the dichloridate, there was a further increase in both the d.e. and overall yield of the desired product. These results show that high diastereoselectivity is possible independent of addition order but that in one aspect the diol and Lewis acid are added to the dichloridate for high diastereoselectivity.

Another aspect found was that using this procedure, the coupling reaction no longer has to be performed at low temperatures.

TABLE 1

EFFECT OF SOLUTION COMPONENTS, TEMPERATURE AND ADDITION ORDER

Entry	Base	Equiv.	Temp (°C)	Addition	*Cis:Trans* Area %	d.e.
1	Bu_3N	4.8	-70 to -65	dichloridate to (diol + base + $TiCl_4$)	59:13	64
4	Et_3N	4.8	-70 to -65	dichloridate to (diol + base + $TiCl_4$)	73:15	66
5	Et_3N	3.1	10 to 15	dichloridate to (diol + $TiCl_4$ + base)	38:7	69
6	Et_3N	4.0	0 to 10	dichloridate to (diol + $TiCl_4$ + base)	22:1	87
2	Bu_3N	4.8	0 to 10	(diol + base) to (dichoridate + $TiCl_4$)	58:11	68
3	Et_3N	4.8	0 to 10	(diol + base) to (dichoridate + $TiCl_4$)	60:14	62
7	Et_3N	4.0	20 to 25	(diol + $TiCl_4$ + base) to dichloridate	76:1	97
8	Et_3N	4.0	Reflux	(diol + $TiCl_4$ + base) to dichloridate	76:6	85
9	Hunig	4.0	18 to 22	(diol + $TiCl_4$ + base) to dichloridate	73:4	90
10	Et_3N	6.0	17 to 19	(diol + $TiCl_4$ + base) to dichloridate	73:3	92
11	Et_3N	9.0	17 to 22	(diol + $TiCl_4$ + base) to dichloridate	74:2	95

5

3. Isolation of Cyclic Phosphonic Ester:

The reaction mixture from the coupling reaction was quenched with methanol and partitioned with water. The acidic aqueous phase containing the

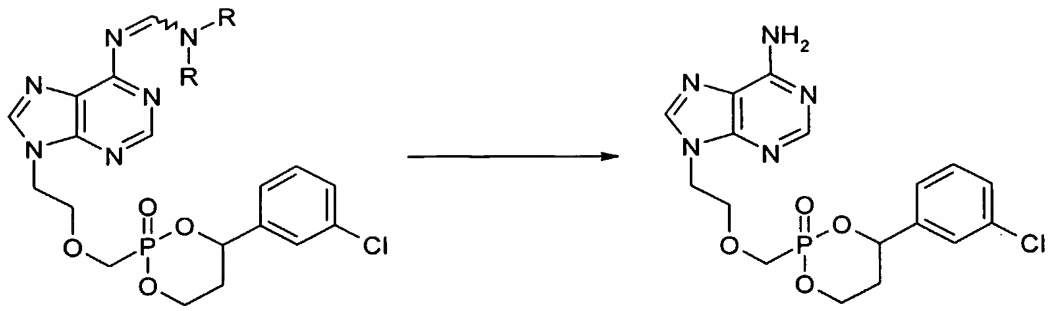
product was extracted several times with chloroform. The combined organic layers were dried and concentrated to an oil, affording the N6 protected form of the cyclic phosphonic ester.

An alternative method of isolation consists of addition of a base (such as triethylamine) to the reaction mixture, resulting in precipitation of salts derived from the Lewis acid. Filtration of the precipitated material is facilitated by the use of a filter aid (*e.g.* diatomaceous earth, Fuller's earth, Montmorillonite clay), after which the filtrate containing the product is concentrated or further manipulated in the usual way (washing with water, extraction of the product into aqueous acid, back-extraction with an organic solvent, etc.).

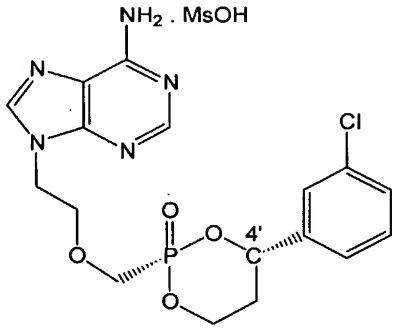
A further aspect of workup involves use of a chelating agent to remove materials derived from the Lewis acid. In one aspect the chelating agent could be a bifunctional organic compound (*e.g.*, TMEDA, tartaric acid, EDTA) that renders the salts derived from the Lewis acid water-soluble, and hence removable by extraction. In another aspect the chelating agent could also be a functionalized solid support (*e.g.*, a polymeric resin containing amine or carboxylic acid functional groups capable of chelation), in which case removal of salts is accomplished by filtration.

4. Crystallization of *cis* Prodrug Salt:

Deprotection of the N6 position of the coupled phosphonic acid and chiral diol is accomplished under mild acidic conditions. The isolated coupling mixture was treated with refluxing acetic acid in ethanol to effect nitrogen deprotection. Crystallization of the resultant product using methanesulfonic acid gave rise to the *cis* prodrug as a mesylate salt (Formula C) with 94-98% chemical purity. The *trans* isomer is the major impurity and a second crystallization of the final material from an alcohol such as methanol gave greater than 96% diastereomeric purity (d.e. from 96 to 99%).



(*cis:trans* = 74:2) (*cis:trans* = 74:2)



Formula C

The use of other acids including but not limited to such as sulfuric, nitric, hydrochloric, phosphoric, sulfonic, tartaric, citric, maleic, malic, malonic, lactic, oxalic acids and the like, may lead to better recovery and isomeric ratio of the product. The protocol as described for PMEA is also applicable to other PME or PMP derivatives.

The compounds used in this invention and their preparation can be understood further by the examples which illustrate some of the processes by which these compounds are prepared. These examples should not however be construed as specifically limiting the invention and variations of the compounds, now known or later developed, are considered to fall within the scope of the present invention as hereinafter claimed.

EXAMPLES

Example 1: Preparation of 3-(3-chlorophenyl)-3-oxo-propanoic acid (1)

The diol was prepared as described in U.S. PreGrant Published Application No. 20030225277A1. A 12 L, 3-neck round bottom flask was equipped with a mechanical stirrer and addition funnel (2 L). The flask was flushed with nitrogen and charged with diisopropylamine (636 mL) and THF (1.80 L). The stirred contents were cooled to –20 °C. n-Butyllithium (1.81 L of a 2.5 M solution in hexanes) was added slowly with stirring, and the temperature was maintained between -20 and –28 °C. After the addition was complete (30 min), the addition funnel was rinsed with hexanes (30 mL) and the stirred solution was then cooled to –62 °C. Trimethylsilyl acetate (300 g) was added slowly with stirring, maintaining the temperature at <-60 °C. After the addition was complete (about 30 min), the solution was stirred at –60 °C for 15 min. 3-Chlorobenzoyl chloride (295 mL) was added slowly with stirring, maintaining the temperature at <-60 °C. After the addition was complete (about 65 min), the cooling bath was removed and the reaction solution was stirred for approximately 1.25 h, with gradual warming to 0 °C. The reaction flask was cooled with an ice bath, then water (1.8 L) was added to the stirred solution. The reaction mixture was stirred for 10 min, and then diluted with *t*-butyl methyl ether (MTBE) (1.0 L). The lower aqueous phase was separated and transferred to a round bottom flask equipped with a mechanical stirrer. MTBE was added (1.8 L) and the stirred mixture was cooled to <10 °C in an ice bath. Concentrated HCl solution (300 mL of 12 M solution) was added and the mixture was vigorously stirred. The layers were separated and the aqueous phase was further acidified with concentrated HCl (30 mL) and extracted again with MTBE (1.0 L). The combined MTBE extracts were washed with approximately 10% NaCl solution (1 L), dried ($MgSO_4$, 70 g), filtered and concentrated under reduced pressure to give 827 g of a yellow solid. The crude solid was slurried in hexanes (2.2 L) and transferred to a round bottom flask equipped with a mechanical stirrer. The mixture was stirred at <10 °C for 1 h, then filtered, washed with hexanes (4 x 100 mL) and dried to constant weight (-30 in. Hg, ambient temperature, 14 h).

Example 2: Preparation of (*S*)-3-(3-Chlorophenyl)-3-hydroxypropanoic acid (2)

The 3-hydroxypropanoic acid was prepared as described in U.S. PreGrant Published Application No. 20030225277A1. A 12 L, 3-neck round bottom flask was equipped with a mechanical stirrer and addition funnel (1 L). The flask was flushed with nitrogen and charged with 3-(3-chlorophenyl)-3-oxo-propanoic acid (275.5 g) **1** and dichloromethane (2.2 L). A thermocouple probe was immersed in the reaction slurry and the stirred contents were cooled to –20 °C. Triethylamine (211 mL) was added over 5 min. to the stirred slurry and all solids dissolved. A dichloromethane solution of (-)-beta-chlorodiisopinocampheylborane (1.60 M, 1.04 L) was charged to the addition funnel, and then added slowly with stirring while maintaining the temperature between –20 and -25 °C. After the addition was complete (approximately 35 min), the solution was warmed to ice bath temperature (2-3 °C) and stirred. After approximately 4 h of stirring an in-process NMR analysis indicated the starting material **1** was <4%.

The residual starting material **1** was measured by proton NMR as follows: removing a 0.5 mL sample of the reaction mixture and quenching with water (0.5 mL) and 3 M NaOH solution (0.5 mL). The quenched mixture was stirred and the layers separated. The aqueous phase was acidified with 2 M HCl (1 mL) and extracted with ethyl acetate (1 mL). The organic phase was separated, filtered through a plug of $MgSO_4$ and concentrated with a stream of nitrogen. The residue was dissolved in CH_2Cl_2 and the solvent was evaporated with a stream of nitrogen. Water (1.2 L) was added to the cloudy orange reaction mixture, followed by 3 M NaOH solution (1.44 L). The mixture was vigorously stirred for 5 min. and then transferred to a separatory funnel. The layers were separated and the basic aqueous phase was washed with ethyl acetate (1 L). The aqueous phase was acidified with concentrated HCl (300 mL) and extracted with ethyl acetate (2 times with 1.3 L each). The two acidic ethyl acetate extracts were combined, washed with approximately 10% NaCl solution (600 mL), dried with $MgSO_4$ (130 g), filtered and concentrated under reduced pressure to provide 328 g of a yellow oil. The oil crystallized upon standing. The resulting solid was slurried in ethyl acetate (180 mL) and transferred to a 2 L, 3-neck round bottom flask, equipped with a mechanical stirrer. The stirred ethyl acetate mixture was cooled

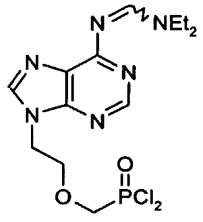
to <10 °C (ice bath), then diluted with hexanes (800 mL). The resulting mixture was stirred at ice bath temperature for 4 h, and then filtered. The collected solid was washed with 4:1 hexanes:ethyl acetate (3 x 50 mL) and dried to constant weight (-30 inches of Hg, ambient temperature, 12 h).

Example 3: Preparation of (*S*)-(-)-1-(3-chlorophenyl)-1,3-propanediol (3)

The diol was prepared as described in U.S. PreGrant Published Application No. 20030225277 A1. A 12 L, 3-neck round bottom flask was equipped with a mechanical stirrer, addition funnel (2 L) and thermometer. The flask was flushed with nitrogen and charged with (*S*)-3-(3-chlorophenyl)-3-hydroxypropanoic acid **2** (206.7 g) and THF (850 mL), and the stirred solution was cooled to 5 °C. (ice bath). A 1 M borane in THF solution (2.14 L) was charged to the addition funnel, and then added slowly with stirring maintaining the temperature at <10 °C. After the addition was complete (approximately 1 h), the cooling bath was removed and the solution was stirred at ambient temperature for 1 h. The reaction solution was slowly and cautiously quenched with water (600 mL), followed by 3 M NaOH solution (850 mL). The mixture was stirred for 10 min. with an observed temperature increase to approximately 40 °C, and then the mixture was transferred to a separatory funnel. The layers were separated and the aqueous phase was extracted again with ethyl acetate (600 mL). The combined organic phase was washed with approximately 10% NaCl solution (500 mL), dried ($MgSO_4$, 322 g), filtered and concentrated under reduced pressure to provide 189.0 g of a pale yellow oil (101%).

Example 4: Preparation 9-{2-[2,4-*cis*-(*S*)-(+)-4-(3-chlorophenyl)-2-oxo-1,3,2-dioxaphosphorinan-2-yl]methoxyethyl}adenine methanesulfonate (9)

Example 4.1: Formation of Dichloridate (8)



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A 250 mL, 4-neck round bottom flask was equipped with a mechanical stirrer, condenser, addition funnel (25 mL) and heating mantle. The flask was flushed with nitrogen and charged with PMEA (15.05 g), dichloromethane (190 mL) and N,N-diethylformamide (6 .15 g). Oxalyl chloride (15.3 mL) was charged to the addition funnel, and added slowly to the stirred reaction mixture at a rate to maintain control over gas evolution (0.5 h.). After the addition was complete (30 min.), the addition funnel was removed and the vigorously stirred mixture was heated at reflux for 4 h.

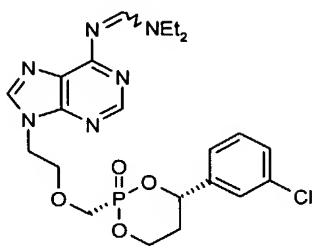
Example 4.2: Coupling Reaction

A 250 mL, 3-neck round bottom flask was equipped with a mechanical stirrer, a cooling bath, nitrogen inlet, thermocouple, and addition funnel (25 mL). The flask was flushed with nitrogen and charged with (*S*)-(-)-(3-chlorophenyl)-1,3-propanediol **3** (10.6 g) and methylene chloride (150 mL). The solution was cooled to <10 °C. Titanium tetrachloride (6.2 mL) was added and a heavy precipitate formed after approximately 5 min. Triethylamine (31 mL) was added, the precipitate dissolved, and the solution turned purple. After a few additional minutes a light precipitate formed. The diol solution containing the titanium tetrachloride was added to the dichloridate solution **8** over a 90 min. period. The initial temperature was 19 °C and the final temperature was 24 °C. The reaction was stirred at ambient temperature for 1 h and then quenched with methanol (90 mL). The *in situ* yield of the *cis* coupled product was 91%. The reaction mixture was washed with water (165 mL) and the layers were separated. The aqueous phase was extracted with chloroform (3 x 150 mL). The combined organic phases were washed with 5% sodium chloride (300 mL). The resultant brine layer contained additional product and was extracted with chloroform (6 x 50 mL). The combined organic phase was dried ($MgSO_4$, 35 g), filtered through diatomaceous earth (Celite 521), and concentrated under reduced pressure to give an oil. The HPLC analysis samples were dissolved in methanol.

HPLC conditions:

YMC-Pack R & D, R-33-5 S-5 120A, 250 X 4.6 mm; mobile phase: Solvent A = 20 mM potassium phosphate, pH 6.2; Solvent B = acetonitrile; gradient: 10-60%B/ 15 min., 60-10%B/ 2 min., 10%B/ 3 min.; 1.4 mL/ min.; inj. vol.= 10 µL; UV detection at 270 nm.

Retention times: *cis* **13** = 12.5 min., *trans* **14** = 13.0 min.



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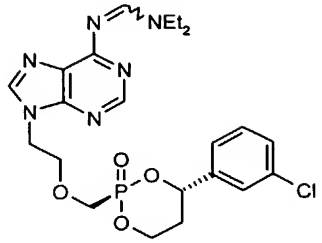

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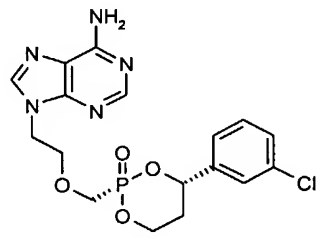
The material was dissolved in ethanol (150 mL) and transferred to a 500 mL round bottom flask equipped with magnetic stirring, condenser and heating mantle. Acetic acid (16.5 mL) was added and the solution was heated at reflux for 8 h. HPLC indicated the reaction was complete. The HPLC samples were dissolved in methanol.

HPLC conditions:

YMC-Pack R & D, R-33-5 S-5 120A, 250 X 4.6 mm; mobile phase: Solvent A = 20 mM potassium phosphate, pH 6.2; Solvent B = acetonitrile; gradient: 10-60%B/ 15 min., 60-10%B/ 2 min., 10%B/ 3 min.; 1.4 mL/ min.; inj. vol.= 10 μL; UV detection at 270 nm.

Retention times: *cis* **15** = 9.5 min., *trans* **16** = 9.8 min.



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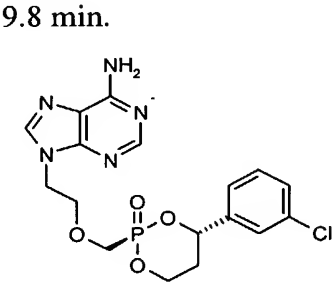

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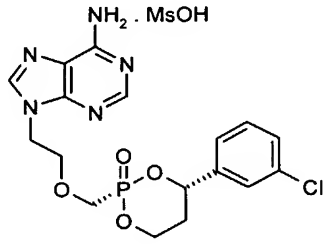
Example 4.3: Crystallization of 9-{2-[2,4-*cis*-(*S*)-(+)-4-(3-chlorophenyl)-2-oxo-1,3,2-dioxaphosphorinan-2-yl]methoxyethyl}adenine methanesulfonate (9)

Methanesulfonic acid (9.03 g) was added and a precipitate formed after 15 min. The mixture was diluted with ethanol (90 mL) and heated until all solids

dissolved (pot temperature = 78 °C). The solution was cooled with stirring and a precipitate formed at 50 °C. The resulting mixture was stirred for 4 h, with cooling to ambient temperature, then at ice bath temperature for 1 h. The mixture was filtered and the collected solid was washed with cool ethanol (2 X 10 mL) and dried to constant weight (-30 in. Hg, 40-50 °C, overnight) to yield a pale yellow solid. Recovery = 19.9 g **9** (70%). The solid *cis:trans* ratio was 97.8:1.7.

Chiral HPLC: Pirkle covalent (S,S) Whelk-O 1 10/100 krom FEC 250 X 4.6 mm; mobile phase = 55:45, methanol: 0.1 % HOAc in water; isocratic; 1.0 mL/ min.; inj. Vol. = 10 μL; UV detection at 260 nm; sample preparation = 2.0 mg/ mL in water. Retention times: *cis*-(*R*) **5** = 24.6 min., *trans*-(*R*) **6** = 27.5 min., *cis*-(*S*) **7** = 18.0 min.

^{1}H NMR (D_2O) was used to confirm structure of components.



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Example 4.4: Recrystallization of 9-{2-[2,4-*cis*-(*S*)-(+)-4-(3-chlorophenyl)-2-oxo-1,3,2-dioxaphosphorinan-2-yl]methoxyethyl}adenine methanesulfonate (9)

A 1 L, 3-neck round bottom flask was equipped with a mechanical stirrer, condenser, heating mantle and thermometer. The flask was charged with the crude mesylate salt **9** and ethanol (400 mL). The stirred mixture was heated at reflux (pot temperature was 78 °C) until all solids dissolved (approximately 10 min.). The stirred mixture was gradually cooled to ambient temperature over 3 h (a precipitate formed at 52 °C). The mixture was stirred at ambient temperature for an additional hour, cooled to 10 °C and stirred for another hour and then filtered. The collected solid was washed with cool ethanol (2 x 10 mL) and dried overnight(-30 in Hg, 45-50 °C, 16 hrs.) .) to yield a pale yellow solid (17.64 g, 62% overall yield). *Cis:trans* ratio = 99.5:0.5.

Color: pale yellow solid

Example 5: Coupling of iodomethylphosphonic acid with (*S*)-(-)-1-(3-chlorophenyl)-1,3-propanediol

A 500 mL 4-neck round bottom flask equipped with a heating mantle, mechanical stirring, an addition funnel, thermocouple, and a condenser with nitrogen inlet was charged with methylene chloride (80 mL), iodomethylphosphonic acid (9.88 g, 44.5 mmol), and N,N-diethylformamide (0.4 mL, 5.0 mol). The oxalyl chloride (9.0 mL, 103 mmol) was added via the addition funnel at such a rate as to maintain control over the gas evolution (0.25 h). The slurry was heated to reflux for 4 h during which time all of the solids had dissolved. The solution was cooled to room temperature. A 100 mL 3-neck round bottom flask equipped with a cooling bath, mechanical stirring, nitrogen inlet, thermocouple, and tubing adapter was charged with methylene chloride (70 mL), *S*(-)-1-(3-chlorophenyl)-1,3-propanediol **3** (8.85 g, 44.6 mmol). The solution was cooled to < 10 °C. Titanium tetrachloride (4.9 ml, 45.6 mmol) was added, and a heavy precipitate formed after approximately 5 min. Triethylamine (25 ml, 178 mmol) was added. The precipitate dissolved, and the solution turned to a purple color. After a few minutes, a light precipitate was observed forming. The diol/titanium tetrachloride solution was added to the dichloridate solution over 15 min; the initial temperature was 20 °C and the final temperature was 25 °C. The reaction was stirred at ambient temperature for 1 h, and then quenched with methanol (10 mL) and water (50 mL). After separation of layers, the aqueous phase was extracted with methylene chloride (50 mL). The combined organic layers were dried over $MgSO_4$, and concentrated to an oil (20 g). The ratio of major to minor isomer = 3.62:1.00 . by ^{31}P NMR (DMSO) δ = 91.0 (3.62 P), 88.6 (1.00P).

Example 6: Preparation of 4-{4-[2,4-*cis*-(*S*)-4-(3-chlorophenyl)-2-oxo-2λ^5-[1,3,2]dioxaphosphinan-2-ylmethoxy]-2,6-dimethylbenzyl}-2-isopropylphenol

A 500 ml 4-neck round bottom flask equipped with a heating mantle, mechanical stirring, an addition funnel, thermocouple, and a condenser with nitrogen inlet is charged with methylene chloride (190 ml), [4-(3-isopropyl-4-triisopropylsilanyloxy-benzyl)-3,5-dimethyl-phenoxymethyl]-phosphonic acid

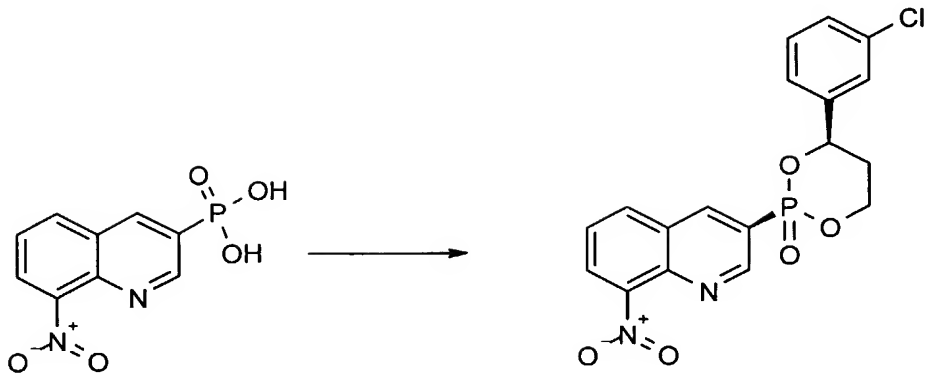
(55.1 mmol), and N,N -diethylformamide (5 mmol). Oxalyl chloride (115 mmol) is added via the addition funnel at a rate to control the gas evolution (0.5 h). The slurry is heated to reflux for 4 h. The solution is cooled to room temperature. A 250 ml 3-neck round bottom flask equipped with a cooling bath, mechanical stirring, nitrogen inlet, thermocouple, and tubing adapter is charged with methylene chloride (150 ml) and *S*(-)-1-(3-chlorophenyl)-1,3-propanediol (55.1 mmol). The solution is cooled to < 10 °C. Titanium tetrachloride (56.0 mmol) is added, and a heavy precipitate forms after approximately 5 min. Triethylamine (222 mmol) is added. The precipitate dissolves, and the solution changes to a purple color. After a few minutes, a light precipitate forms. The diol/titanium tetrachloride solution is added to the dichloridate solution over 90 min. The reaction is stirred at ambient temperature for 1 h, and then is quenched with methanol (90 ml). The *cis:trans* ratio is approximately 3 to 1. The solution is poured into water (165 ml). The mixture is transferred to a separatory funnel, and the layers are separated. The organic phase is washed with 5% sodium chloride solution (300 ml) and is dried over $MgSO_4$. The methylene chloride is removed by vacuum distillation. THF (300 ml) and tetrethylammonium fluoride (56 mmol) is added. The solution is stirred for 1 h followed by quenching with water (50 ml). After separation of layers, the aqueous phase is extracted with ethyl acetate (50 ml). The combined organic layers are washed with brine (50 ml), dried over $MgSO_4$, and are concentrated. The product, 4-{4-[2,4-*cis*-(*S*)-4-(3-chlorophenyl)-2-oxo-2λ^5-[1,3,2]dioxaphosphinan-2-ylmethoxy]-2,6-dimethylbenzyl}-2-isopropylphenol is purified by crystallization or chromatography.

Example 7. Preparation of 4-{4-[2,4-*cis*-(*S*)-4-(3,5-dichlorophenyl)-2-oxo-2λ^5-[1,3,2]dioxaphosphinan-2-ylmethoxy]-2,6-dimethylbenzyl}-2-isopropylphenol

A 500 ml 4-neck round bottom flask equipped with a heating mantle, mechanical stirring, an addition funnel, thermocouple, and a condenser with nitrogen inlet is charged with methylene chloride (190 ml), [4-(3-isopropyl-4-triisopropylsilanyloxy-benzyl)-3,5-dimethyl-phenoxymethyl]-phosphonic acid (55.1 mmol), and N,N-diethylformamide (5 mmol). Oxalyl chloride (115 mmol)

is added via the addition funnel at a rate to maintain control over the gas evolution (0.5 h). The slurry is heated to reflux for 4 h. The solution is cooled to room temperature. A 250 ml 3-neck round bottom flask equipped with a cooling bath, mechanical stirring, nitrogen inlet, thermocouple, and tubing adapter is charged with methylene chloride (150 ml) and *S*(-)-1-(3,5-dichlorophenyl)-1,3-propanediol (55.1 mmol). The solution is cooled to < 10 °C. Titanium tetrachloride (56.0 mmol) is added, and a heavy precipitate forms after approximately 5 min. Triethylamine (222 mmol) is added. The precipitate dissolves, and the solution exhibits a color change to purple. After a few minutes, a light precipitate forms. The diol/titanium tetrachloride solution is added to the dichloridate solution over 90 min. The reaction is stirred at ambient temperature for 1 h, and then quenched with methanol (90 ml). The *cis:trans* ratio is approximately 3 to 1. The solution is poured into water (165 ml). The mixture is transferred to a separatory funnel, and the layers are separated. The organic phase is washed with 5% sodium chloride solution (300 ml) and dried over $MgSO_4$. The methylene chloride is removed by vacuum distillation. THF (300 ml) and tetraethylammonium fluoride (56 mmol) is added. The solution is stirred for 1 h, and is then quenched with water (50 ml). After separation of layers, the aqueous phase is extracted with ethyl acetate (50 ml). The combined organic layers are washed with brine (50 ml), dried over $MgSO_4$, and is concentrated. The product, 4-{4-[2,4-*cis*-(*S*)-4-(3,5-dichlorophenyl)-2-oxo-2λ^5-[1,3,2]dioxaphosphinan-2-ylmethoxy]-2,6-dimethylbenzyl}-2-isopropylphenol is purified by crystallization or chromatography.

Example 8. Preparation of 8-Nitro-3-[2,4-cis-4-(3-chlorophenyl)-2-oxo-1,3,2-dioxaphosphorinanyl]quinoline



In a 250 mL r.b. flask, (15 mmol) of 8-nitroquinoline-3-phosphonic acid HBr salt suspended in 1,2-dichloroethane (50 mL) was combined with (37 mmol) oxalyl chloride and DMF (300 uL). The slurry was refluxed for 4 hrs then allowed to cool to rt. In a second r.b. flask, (15 mmol) of (3-chlorophenyl)-1,3-propanediol was dissolved in methylene chloride (40 mL) and cooled to -78 °C. To this solution was added (15.2 mmol) of $TiCl_4$. After stirring for 5 min at 0 °C, (60 mmol) of triethylamine was slowly added and the resulting mixture stirred for an additional 2 min. The diol mixture was added via addition funnel to the dichloridate solution over a period of 1 hr then allowed to stir at rt overnight. The reaction mixture was quenched by adding MeOH (20 mL), stirring for 20 min then combining with 10% aqueous tartaric acid solution. After stirring for 30 more min, TMEDA (20 mL) was added (exothermic!) followed by ice water and the layers separated. The aqueous portion was extracted with methylene chloride (2 x 100 mL), the organics combined, dried over Na_2SO_4 and concentrated under vacuum to afford the crude product. Flash chromatography (SiO_2) using DCM/MeOH (60:1 to 40:1) as the eluting gradient gave 3.3 g of product as a 25:1 cis/trans mixture. ^{31}P NMR (DMSO) δ = 11.12 (cis), 7.19 (trans).

We claim:

1. A method of preparing a cyclic phosphonic acid diester comprising:

reacting a chiral 1,3-diol and an activated phosphonic acid in the presence of a Lewis acid.

2. The method of claim 1 wherein said Lewis acid is added to said chiral 1,3-diol and the diol-Lewis acid complex is added to said activated phosphonic acid.

3. The method of claim 1 wherein the ratio of *cis*- to *trans*-diastereomers formed is greater than or equal to 3:1.

4. The method of claim 1 wherein said Lewis acid contains an element selected from the group consisting of titanium, tin, aluminum, zinc, boron, magnesium, samarium, bismuth, iron, mercury, copper, silver, and cobalt.

5. The method of claim 4 wherein said element is selected from the group consisting of titanium, boron, aluminum, tin, and samarium.

6. The method of claim 5 wherein said Lewis acid contains a group independently selected from the group consisting of alkoxy, alkyl , aryl, and an inorganic radical.

7. The method of claim 6 wherein said inorganic radical is selected from the group consisting of chloride, iodide, bromide, and fluoride.

8. The method of claim 7 wherein said Lewis acid is selected from the group consisting of $TiCl_4$, BF_3, $SnCl_4$, SmI_2, and $AlCl_3$.

9. The method of claim 8 wherein said Lewis acid is $TiCl_4$.

10. The method of claim 5 wherein said Lewis acid is $Ti(O\text{-}(C_1\text{-}C_4)alkyl)_4$.

11. The method of claim 1 wherein said activated phosphonic acid is selected from the group consisting of phosphonic acid halide, phosphonic acid anhydride, and phosphonic acid carbonate.

12. The method of claim 11 wherein said activated phosphonic acid is a phosphonic acid halide.

13. The method of claim 12 wherein said phosphonic acid halide is a phosphonyl chloride.

14. The method of claim 1 further comprising adding a base selected from the group consisting of tertiary alkyl amines, N-containing heterocyclic aromatic bases, and non-nucleophilic inorganic bases.

15. The method of claim 14 wherein said base is selected from the group consisting of triethylamine, tri(n-butyl)amine, pyridine, quinoline, and diisopropylethylamine.

16. The method of claim 1 wherein the temperature for the reaction is between -78 °C and 60 °C.

17. The method of claim 16 wherein said temperature is between -20 °C and 50 °C.

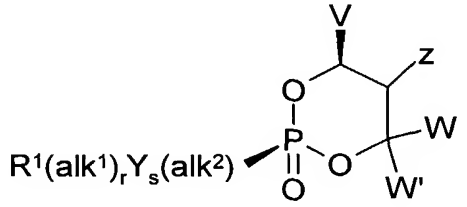
18. The method of claim 17 wherein said temperature is between 15 °C and 42 °C.

19. The method of claim 1 further comprising:

adding 0.01 to 5 equivalents of said Lewis acid to 1.0 equivalent of said chiral 1,3-diol.

20. The method of claim 19 wherein 0.5 to 2.0 equivalents of said Lewis acid is added.

21. A method for the preparation of compounds of Formula I:



Formula I

wherein:

V is selected from group consisting of phenyl, allyl, alkynyl, and monocyclic heteroaryl, all optionally substituted with 1-4 substituents;

R^1 is selected from the group consisting of hydrogen, optionally substituted aryl, optionally substituted heteroaryl, or

R^1 is a group of the formula Ar^1-G-Ar^2, wherein Ar^1 and Ar^2 are aryl groups optionally substituted by lower alkyl, lower alkoxy, halogen, hydroxy, cyano, and amino, and G is -O-, -S-, -S(=O)-, -$S(=O)_2$-, -CH_2-, -CF_2-, -CHF-, -C(O)-, -CH(OH)-, -NH-, and -N(C_1-C_4 alkyl)-;

alk^1 and alk^2 are the same or different and are each optionally substituted lower alkylene;

Y is selected from the group consisting of –O-, -S-, $-NR^2-$, -C(O)-, $-C(O)NR^2$, and $-NR^2C(O)-$;

W and W' are independently selected from the group consisting of H, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted monocyclic aryl, and optionally substituted monocyclic heteroaryl;

Z is selected from the group consisting of halogen, -CN, $-COR^3$, $-CONR^4_2$,
$-CO_2R^3$, $-CHR^2OC(O)R^3$, $-CHR^2OC(S)R^3$, $-CHR^2OC(O)SR^3$, $-CHR^2OCO_2R^3$, $-OR^3$,
$-SR^3$, $-R^2$, $-NR^3_2$, $-OCOR^3$, $-OCO_2R^3$, $-SCOR^3$, $-SCO_2R^3$, $-(CH_2)_p-OR^4$, and $-(CH_2)_p-SR^4$;

R^2 is hydrogen or lower alkyl;

R^3 is alkyl;

R^4 is alkyl or acyl;

p is 2 or 3;

r is 0 or 1; and

s is 0 or 1;

comprising:

reacting a 1-(aryl)-1,3-propane diol with $R^1(alk^1)_rY_s(alk^2)P(O)Cl_2$ in the presence of a base and a Lewis acid.

22. The method of claim 21 wherein said 1-(aryl)-1,3-propane diol is added to said Lewis acid and then the diol-Lewis acid complex is added to $R^1(alk^1)_rY_s(alk^2)P(O)Cl_2$ in the presence of said base.

23. The method of claim 21 wherein the ratio of *cis*- to *trans*-diastereomers formed is greater than or equal to 3:1.

24. The method of claim 21 wherein said Lewis acid is an acid containing an element selected from the group consisting of titanium, tin, aluminum, zinc, boron, magnesium, samarium, bismuth, iron, mercury, copper, silver, and cobalt.

25. The method of claim 24 wherein said element is selected from the group consisting of titanium, boron, aluminum, tin, and samarium.

26. The method of claim 25 wherein said Lewis acid contains a group independently selected from the group consisting of alkoxy, alkyl , aryl, and an inorganic radical.

27. The method of claim 26 wherein said inorganic radical is selected from the group consisting of chloride, bromide, iodide, and fluoride.

28. The method of claim 27 wherein said Lewis acid is selected from the group consisting of $TiCl_4$, BF_3, $SnCl_4$, SmI_2, and $AlCl_3$.

29. The method of claim 28 wherein said Lewis acid is $TiCl_4$.

30. The method of claim 25 wherein said Lewis acid is $Ti(O\text{-}(C_1\text{-}C_4)alkyl)_4$.

31. The method of claim 21 wherein said base is selected from the group consisting of tertiary alkyl amines, N-containing heterocyclic aromatic bases, and non-nucleophilic inorganic bases.

32. The method of claim 31 wherein said base is selected from the group consisting of triethylamine, tri(n-butyl)amine, pyridine, quinoline, and diisopropylethylamine.

33. The method of claim 21 wherein the temperature for the reaction is between -78 °C and 60°C.

34. The method of claim 33 wherein said temperature is between -20 °C and 50 °C.

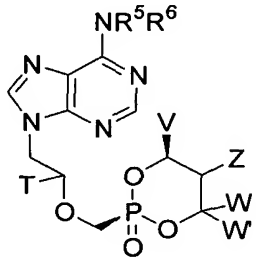
35. The method of claim 34 wherein said temperature is between 15 °C and 42 °C.

36. The method of claim 21 further comprising:

adding 0.01 to 5 equivalents of said Lewis acid to 1.0 equivalent of said 1-(V)-1,3-propane diol.

37. The method of claim 36 wherein 0.5 to 2.0 equivalents of said Lewis acid is added.

38. A method for the preparation of compounds of Formula II:



Formula II

wherein:

V is selected from group consisting of aryl, and monocyclic heteroaryl, all optionally substituted with 1-4 substituents;

W and W' are independently selected from the group consisting of H, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted monocyclic aryl, and optionally substituted monocyclic heteroaryl;

Z is selected from the group consisting of halogen, -CN, $-COR^3$, $-CONR^4_2$,
$-CO_2R^3$, $-CHR^2OC(O)R^3$, $-CHR^2OC(S)R^3$, $-CHR^2OC(O)SR^3$, $-CHR^2OCO_2R^3$, $-OR^3$,
$-SR^3$, $-R^2$, $-NR^3_2$, $-OCOR^3$, $-OCO_2R^3$, $-SCOR^3$, $-SCO_2R^3$, $-(CH_2)_p-OR^4$, and $-(CH_2)_p-SR^4$;

T is selected from the group consisting of H and lower alkyl;

R^2 is hydrogen or lower alkyl;

R^3 is alkyl;

R^4 is alkyl or acyl;

p is 2 or 3;

r is 0 or 1, and

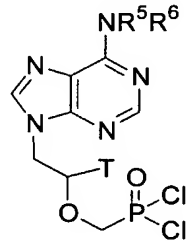
s is 0 or 1;

R^5 is a monovalent amine protecting group, and R^6 is hydrogen; or,

R^5 and R^6 taken together are a divalent amine protecting group;

comprising:

combining a 1-(V)-1,3-propane diol with a compound of Formula III in the presence of a Lewis acid:



Formula III.

39. The method of claim 38 wherein said 1-(V)-1,3-propane diol is added to said Lewis acid and then the diol-Lewis acid complex is added to said compound of Formula III.

40. The method of claim 38 wherein said Lewis acid is selected from the group consisting of $TiCl_4$, BF_3, $SnCl_4$, SmI_2, and $AlCl_3$.

41. The method of claim 40 wherein said Lewis acid is $TiCl_4$.

42. The method of claim 38 wherein said Lewis acid is $Ti(O\text{-}(C_1\text{-}C_4)alkyl)_4$.

43. The method of claim 38 wherein the ratio of *cis*- to *trans*-diastereomers formed is greater than or equal to 3:1.

44. The method of claim 38 further comprising adding a base selected from the group consisting of tertiary alkyl amines, N-containing heterocyclic aromatic bases, and non-nucleophilic inorganic bases.

45. The method of claim 44 wherein said base is selected from the group consisting of triethylamine, tri(n-butyl)amine, pyridine, quinoline, and diisopropylethylamine.

46. The method of claim 38 wherein the temperature for the reaction is between -78 °C and 60 °C.

47. The method of claim 46 wherein said temperature is between -20 °C and 50 °C.

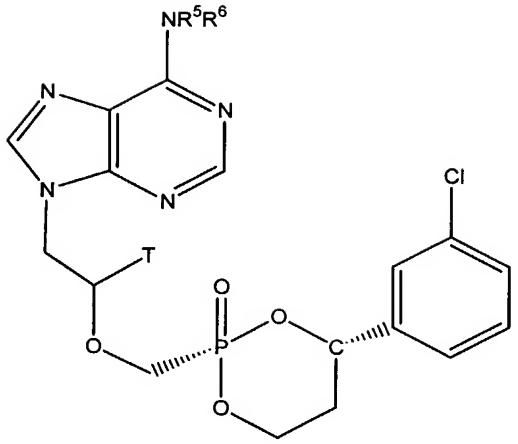
48. The method of claim 47 wherein said temperature is between 15 °C and 42 °C.

49. The method of claim 38 further comprising:

adding 0.01 to 5 equivalents of said Lewis acid to 1.0 equivalent of said 1-(V)-1,3-propane diol.

50. The method of claim 49 wherein 0.5 to 2.0 equivalents of said Lewis acid is added.

51. A method for the preparation of compounds of Formula IV:



Formula IV

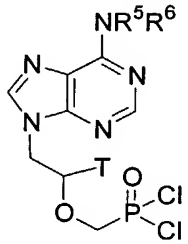
wherein R^5 is *tert*-butyloxycarbonyl, benzyloxycarbonyl, trifluoroacetyl or benzyl, and R^6 is hydrogen; or,

R^5 and R^6 taken together are phthalimidoyl, phenylmethylidene, dimethylaminomethylidene and diethylaminomethylidene;

T is selected from the group consisting of H and lower alkyl;

comprising:

combining (*R*)-1-(3-chlorophenyl)-1,3-propanediol with a compound of Formula III in the presence of a Lewis acid



Formula III.

52. The method of claim 51 wherein said (*R*)-1-(3-chlorophenyl)-1,3-propanediol is added to said Lewis acid and then the diol-Lewis acid complex is added to said compound of Formula III.

53. The method of claim 51 wherein the ratio of *cis*- to *trans*-diastereomers formed is greater than or equal to 3:1.

54. The method of claim 51 wherein said Lewis acid contains an element selected from the group consisting of titanium, tin, aluminum, zinc, boron, magnesium, samarium, bismuth, iron, mercury, copper, silver, and cobalt.

55. The method of claim 54 wherein said element is selected from the group consisting of titanium, boron, aluminum, tin, and samarium.

56. The method of claim 55 wherein said Lewis acid contains a group independently selected from the group consisting of alkoxy, alkyl , aryl, and an inorganic radical.

57. The method of claim 56 wherein said inorganic radical is selected from the group consisting of chloride, iodide, bromide, and fluoride.

58. The method of claim 57 wherein said Lewis acid is selected from the group consisting of $TiCl_4$, BF_3, $SnCl_4$, SmI_2, and $AlCl_3$.

59. The method of claim 58 wherein said Lewis acid is $TiCl_4$.

60. The method of claim 55 wherein said Lewis acid is $Ti(O\text{-}(C_1\text{-}C_4)alkyl)_4$.

61. The method of claim 51 further comprising adding a base selected from the group consisting of tertiary alkyl amines, N-containing heterocyclic aromatic base, and non-nucleophilic inorganic bases.

62. The method of claim 61 wherein said base is selected from the group consisting of triethylamine, tri(n-butyl)amine, pyridine, quinoline, and diisopropylethylamine.

63. The method of claim 51 wherein the temperature for the reaction is between -78 °C and 60 °C.

64. The method of claim 63 wherein said temperature is between -20 °C and 50 °C.

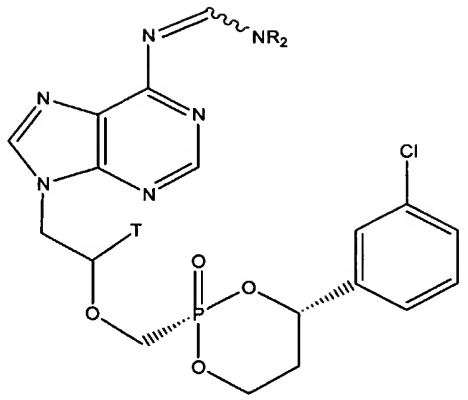
65. The method of claim 64 wherein said temperature is between 15 °C and 42 °C.

66. The method of claim 51 further comprising:

adding 0.01 to 5 equivalents of said Lewis acid to 1.0 equivalent of said (*R*)-1-(3-chlorophenyl)-1,3-propanediol.

67. The method of claim 66 wherein 0.5 to 2.0 equivalents of said Lewis acid is added.

68. A method for the preparation of compounds of Formula V:



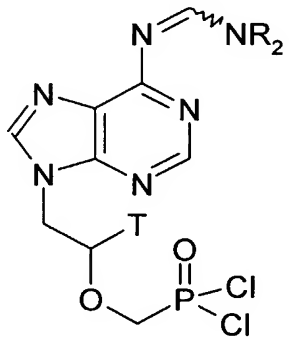
Formula V

wherein R is lower alkyl;

T is selected from the group consisting of H and lower alkyl;

comprising:

combining (*R*)-1-(3-chlorophenyl)-1,3-propanediol with said compound of Formula VI in the presence of a Lewis acid:



Formula VI.

69. The method of claim 68 wherein said (*R*)-1-(3-chlorophenyl)-1,3-propanediol is added to said Lewis acid and then the diol-Lewis acid complex is added to said compound of Formula VI.

70. The method of claim 68 wherein the ratio of *cis*- to *trans*-diastereomers formed is greater than or equal to 3:1.

71. The method of claim 68 wherein said Lewis acid contains an element selected from the group consisting of titanium, tin, aluminum, zinc, boron, magnesium, samarium, bismuth, iron, mercury, copper, silver, and cobalt and contains a group independently selected from the group consisting of alkoxy, alkyl , aryl, and an inorganic radical wherein said inorganic radical is selected from the group consisting of chloride, iodide, bromide, and fluoride.

72. The method of claim 71 wherein said Lewis acid is selected from the group consisting of $TiCl_4$, BF_3, $SnCl_4$, SmI_2, and $AlCl_3$.

73. The method of claim 72 wherein said Lewis acid is $TiCl_4$.

74. The method of claim 71 wherein said Lewis acid is $Ti(O\text{-}(C_1\text{-}C_4)alkyl)_4$.

75. The method of claim 68 further comprising adding a base selected from the group consisting of tertiary alkyl amines, N-containing heterocyclic aromatic base, and non-nucleophilic inorganic bases.

76. The method of claim 75 wherein said base is selected from the group consisting of triethylamine, tri(n-butyl)amine, pyridine, quinoline, and diisopropylethylamine.

77. The method of claim 68 wherein said temperature is between 15 °C and 42 °C.

78. The method of claim 68 further comprising:

adding 0.01 to 5 equivalents of said Lewis acid to 1.0 equivalent of said (*R*)-1-(3-chlorophenyl)-1,3-propanediol.

79. The method of claim 78 wherein 0.5 to 2.0 equivalents of said Lewis acid is added.

INTERNATIONAL SEARCH REPORT

PCT/US05/19440

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) : C07D 471/02; C07F 9/06, 9/28
US CL : 546/23, 117
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 546/23, 117

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EAST; STN: CasReact

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PRISBE E.J. Journal Medical Chemistry, 1986, Vol 29. No. 5, pages 671-675, epsecially page 672.	1-79
Y	FUREGATI S. Helvetica Chimica Acta, 1998, Vol. 81, pages 1127-1138.	1-79
Y	SCHLACHTER S.T. Bioorganic & Medicinal Chemistry Letters, 1998, Vol. 8, pages 1093-1096.	1-79

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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Date of the actual completion of the international search
01 September 2005 (01.09.2005)

Date of mailing of the international search report
06 OCT 2005

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